

Editorial

Brain damage during open-heart surgery

The incidence of neurological dysfunction following cardiac surgical procedures using cardiopulmonary bypass has been estimated at between 15% and 44%.¹⁻³ Despite many improvements in bypass technology in recent years neurological dysfunction remains an important complication and in severe cases may result in a persistent disturbance of cerebral function which nullifies the overall clinical benefit of the cardiac surgical repair. Many research workers have begun to document the clinical characteristics and psychological patterns associated with such damage, while others have focused on the investigation of the major causes.

In the first place it is important to distinguish between lesser degrees of damage and the clinical syndromes of major cellular damage in the brain associated with massive cerebral embolism of air, calcium, particulate matter, and so on. In such patients the cerebral damage is commonly manifested by delay in the return of full consciousness in the immediate postoperative period and the appearance of hemiplegia, associated dysphasia, and sometimes visual disturbance. Where such massive embolic damage has occurred recovery from the focal lesions is often incomplete and residual neurological deficit is apparent. These major events are not the primary subject of this article, which will focus on the less dramatic but much more common syndromes of cerebral dysfunction seen after open-heart surgery. In this syndrome the cerebral damage appears to be much more diffuse and less severe. Though impairment of the level of consciousness after operation may occur, it is usually transitory and persistent cerebral dysfunction tends to result in minor degrees of intellectual impairment, memory loss, and a degree of personality change, a feature often noticed by relatives. Though such cerebral dysfunction is not life threatening it is clearly a major cause for concern in view of the considerable handicap and suffering it may inflict, and much research is at present concerned with it.

Most authorities would agree that the principal causes of this diffuse cerebral damage are, firstly, the altered characteristics of cardiopulmonary bypass perfusion and, secondly, the occurrence of diffuse microembolism. There is already much evidence to implicate both factors in the pathogenesis of the

subsequent cerebral cellular damage. Recent studies suggest, not surprisingly, that cerebral cellular damage represents a combination of perfusion injury and microembolic injury.

Perfusion-related cerebral injury

Knowledge of the changes occurring in cerebral blood flow patterns during cardiopulmonary bypass is far from comprehensive. There have been few attempts in recent years to define the patterns of cerebral blood flow and the responsiveness of cerebral blood flow autoregulation under conditions of total extracorporeal circulation. Some studies have suggested that the cerebral arterioles are reduced to half their normal diameter with the onset of non-pulsatile perfusion⁴ and that capillary flow⁵ and cerebral cellular oxygen consumption and glucose utilisation⁶ are considerably reduced during periods of total-body non-pulsatile perfusion. Non-pulsatile perfusion has also been shown to be associated with appreciable disturbance of hypothalamic-pituitary response patterns.⁷⁻¹² Irreversible hypoxic brain damage may occur when the perfusion of certain areas of the brain falls below critical ischaemic thresholds. The characteristic pattern of selective histological vulnerability has been well described, being concentrated along the boundary zones between the arterial territories of the cerebrum and cerebellum, the so-called watershed areas.¹³ Some authors have suggested that irreversible cerebral cellular damage may occur when the mean arterial perfusion pressure falls below 50–60 mm Hg.¹⁴ The brain is probably much more resistant, however, to reduced perfusion pressure than was previously recognised. Recent studies have failed to show any watershed area of ischaemia in normothermic dogs perfused for two hours at a mean perfusion pressure of 30 mm Hg (Taylor, 1982, unpublished data). The resistance of the brain to reduced perfusion pressure and to a lesser extent reduced flow is in accordance with the consensus of neurophysiological opinion, which would accept in general terms Astrup's proposed scheme of cerebral ischaemia.¹⁵ This indicates that irreversible cell death does not occur until cerebral blood flow falls below 20% of normal values, even at normal body temperature. Hypo-

thermia offers considerable protection in conditions of low-flow, low-pressure perfusion, as recent studies have indicated.¹⁶

The phenomenon of autoregulation of cerebral blood flow is well documented in published reports. Guyton *et al* defined such autoregulation as "the continuous local adjustment of blood flow in proportion to the need of the tissue for nutrients."¹⁷ Though autoregulation of cerebral blood flow is likely to be maintained at least in part during the altered perfusion of total cardiopulmonary bypass, documentation of the patterns of change of cerebral blood flow during bypass and redefinition of the thresholds of pressure, flow, and the effect of pulsatility in bypass perfusion are clearly of crucial importance.

Microembolic cerebral injury

The occurrence of particulate microembolism during cardiopulmonary bypass is well substantiated and is regarded by many as an important cause of cerebral dysfunction after bypass operations. The particles may consist of air,^{18 19} silicone,²⁰ fat,^{21 22} platelet aggregates,²³ and fibrin.²⁴ Where blood cell aggregates are liberated as microemboli, cell injury additional to that produced by obstruction of small arterioles may occur. Electron-microscopy studies have shown that mast cells retained in such aggregates extrude their secretory granules from the cell surface, liberating histamine, kinins, serotonin, and other potentially injurious substances.²⁵ Considerable attention has been directed towards both the prevention and the generation of microembolic debris and also to the trapping of such debris before the arterial blood is returned into the patient's circulation. The proposed adoption of membrane oxygenation^{26 27} and the use of platelet activation inhibitor substances such as prostacyclin^{28 29} are designed to prevent microembolism. Incorporation of a micropore filter in the arterial return line not only reduces particle counts in the arterial line downstream from the filter³⁰⁻³² but also is associated with a reduction in postoperative cerebral dysfunction. Visual-motor test scores have improved³¹ and the cerebral metabolic uptake of oxygen and glucose has increased,⁶ while electrophysiological abnormality² and intellectual impairment¹ have been reduced.

Measurement of cerebral injury

Further progress in the understanding of the pathophysiology of cerebral cellular damage during cardiopulmonary bypass continues to be hampered by the lack of reliable, objective, and sensitive investigative models. Clearly sensitivity in detection of cerebral

cellular damage is of vital importance. So also is the ability to study the cellular dysfunction during or immediately after the period of extracorporeal circulation.

Psychometric testing, electrophysiological assessment, and histological studies have not proved to be sufficiently sensitive or to be particularly applicable in the acute phase. Recently, however, new methods of measuring cerebral injury during open-heart surgical procedures have been developed, based on the direct measurement of cerebrospinal fluid biochemical markers.³³ Early studies have shown that the measurement of cerebrospinal fluid markers in dogs and in patients has a high degree of sensitivity and reproducibility, and in pilot studies the use of arterial line filtration and the substitution of pulsatile perfusion have been associated with considerable reductions in the levels of cerebrospinal fluid markers.³³ Pharmacological pretreatment has also been investigated with these models, steroids giving protection against brain cell injury during perfusion.³⁴ Different biochemical markers have been studied. Creatine kinase with its brain-specific CKB isoenzyme has been used in several studies and has been shown in other contexts to reflect the magnitude of cerebral injury.³⁵⁻³⁹ Other possible markers have been investigated, including the brain amines β -endorphin and enkephalin. Early studies have suggested, however, that the assay techniques for β -endorphin and enkephalin are not at present sufficiently sensitive to allow their use as accurate markers of brain cell injury during open-heart surgery. Of more interest is the neurospecific myelin basic protein that is currently under investigation. Early results appear encouraging. Myelin basic protein may be detected in the cerebrospinal fluid in experimental animals and, more important, may be a possible serum marker of brain cell injury for use in clinical studies.^{40 41} Aberg's group in Scandinavia is studying the enzyme adenylate kinase and confirming the patterns of change shown in my early studies with other biochemical markers.⁴² The sensitivity of the biochemical marker technique is increasingly seen to help the assessment and modification of the cerebral injury associated with open-heart surgical procedures.

Prevention of cerebral damage

Increased attention is currently being paid to cerebral damage as a principal cause of the morbidity after open-heart surgery and many research teams throughout the world are focusing their attention on ways in which it may be reduced. Greater understanding of the pattern of changes in cerebral blood flow during cardiopulmonary bypass should lead to

the definition of safe thresholds of flow, pressure, and pulsatility, so that cerebral perfusion may be optimal during the bypass. Early reports of the effects of pulsatile and non-pulsatile perfusion on cerebral histology^{43,44} require confirmation and further study. In addition, increased awareness of concomitant cerebrovascular disease in patients undergoing cardiopulmonary bypass is likely to clarify the correct perfusion regimens for such patients, since the presence of critical carotid stenoses may considerably impair cerebral perfusion. For the prevention of microembolic damage there is a steady move towards the use of membrane oxygenators, combined with cardiotomy and arterial line filters, in an attempt both to prevent and to trap particulate or gaseous microaggregates generated in the bypass circuit. Increasing attention is now being paid to more accurate control of heparinisation during bypass procedures and also the evaluation of agents such as prostacyclin designed to reduce platelet aggregation. Possibly new systems designed to compute dose-response curves for heparin and protamine dosage during bypass, combined with the use of platelet aggregation inhibitors, will result in appreciable reduction of the overall microaggregate assault on the cerebral circulation. In addition, with further evaluation a pharmacological approach—corticosteroid pretreatment or the use of serotonin antagonists—may be shown to protect the brain, though at present there is little objective evidence that steroid pretreatment offers any appreciable protection in cases of vasogenic cerebral oedema.^{45,46} Improvements in anaesthetic technique continue to contribute greatly to the reduction of bypass-related morbidity. With the present multidisciplinary approach to the problem of brain cell injury during open-heart surgery, greater understanding seems certain to lead eventually to a significant reduction in morbidity.

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